REMARKS

Claim Amendments

Claims 29-39 have been amended to place them in condition for allowance. Support for the amendments to the claims is replete in the specification.

Status

Claims 29-44 are under examination and stand rejected as allegedly obvious in view of U.S. Pat. No. 6,121,029 ("Schupp"), U.S. Pat. No. 6,391,594 ("Khosla A") and WO 97/02358 ("Khosla B"). Applicants respectfully traverse.

The Schupp reference provides nucleotide sequence of the *Sorangium cellulosum* epothilone synthase gene cluster and proposes functions for the encoded proteins, but does not describe the compounds epothilone C and D and, moreover, erroneously teaches that an exogenous (non-cluster) gene product (a methyltransferase) is required to form epothilone B. The pioneering Khosla A reference provides guidance for manipulation, modification, and expression of polyketide synthases generally, but does not describe the epothilone PKS gene cluster, modified epothilone synthases, or epothilone biosynthesis. The Khosla B reference describes synthesis of modified polyketide synthases using cell-expression systems, but does not describe the epothilone PKS gene cluster, modified epothilone synthases, or epothilone biosynthesis.

In part, the claim rejection by the Office appears to be premised on the belief that "the claimed modified epoD have not produced any unexpected results or compounds that would not have been expected from the teachings of [the] gene cluster of epothilone taught by Schupp et al., and the teaching of modifying various activities of similar PKS from the DEBS gene cluster." The Applicants respectfully submit that as EpoD functions in the context of a multiprotein synthase, and as the claims are to a PKS comprising a modified EpoD, the claimed modified synthase does produce results and compounds that would not have been expected from the Schupp reference combined with the teachings of modifying activities of the DEBS gene cluster. To expedite allowance of claims to certain of those compounds or in any event narrow the issues for appeal, the Applicants have amended the claims to recite that the modified EpoD gene product is in a non-

Sorangium host cell that produces the other epothilone PKS proteins and that that PKS produces an epothilone D derivative. Because the Schupp et al. reference teaches that a non-epothilone gene cluster methyltransferase gene is required to place the C-12 methyl in epothilone B and does not even mention epothilone D (which Applicants teach is a precursor of epothilone B), the combination of references cited by the Examiner would not have led the ordinarily skilled artisan to believe that epothilone D derivatives could be produced in non-Sorangium heterologous host cells using an epothilone PKS with a modified epoD gene. Instead, such artisans would have believed that it was impossible to make epothilone B (much less epothilone D) in a heterologous host using the PKS genes described by the Schupp et al. reference.

The present invention provides guidance for making modified epothilone synthases and teaches that such synthases are useful for production of epothilone D derivatives. In contrast, the Schupp reference, while providing sequences corresponding to the epothilone synthase, did not teach what products are produced by the epothilone PKS, without post-synthesis modification by polyketide modifying enzymes. For example, with regard to epothilone A, the Schupp specification contains disclosure relating to formation of an epothilone in which the "redox state" of the C-3 (column 34, lines 42-67), C-5 (see column 33, line 62, through column 34, line 27), and C-12 (see column 33, lines 20-35) carbons of the epothilone macrolactone ring might require "adjustment" by the EPO F gene product to be identical to epothilone A. While the Schupp reference states that "the nascent polyketide chain of epothilone corresponds to epothilone A" (see column 33, lines 30-31), the specification of the Schupp reference creates considerable uncertainty as to what is meant by "corresponds" in this context due to the uncertainty regarding the "redox state" at C-3, C-5, and C-12, and the role of the "EPO F" gene in the "adjustment of the redox state" at one or more of those positions (see column 35, lines 15-20). Similarly, the Schupp patent attributes the origin of the C-12 methyl group that characterizes epothilone B (and therefore, as Applicants but not the Schupp et al. reference taught, epothilone D) as "requiring a post-PKS C-methyltransferase activity." See column 33, lines 31 through 33. The Schupp reference did not disclose the production of epothilone B and epothilone D by the epothilone synthase (teaching instead that a hypothetical post-PKS C-methyltransferase is required) and did not disclose or suggest that epothilone D derivatives would be produced by a modified epothilone synthase. In contrast, the present inventors disclosed that a

product of the epothilone synthase was epothilone D, and that useful derivatives of epothilone D could be made using a synthase comprising a modified EpoD protein that lacks certain β-carbonyl modifying activities of the native protein.

The present inventors provide specific guidance about the results of particular modifications of the EpoD gene (see, e.g., pages 31-41 of the specification) and thus provide motivation *not found* in the cited references to make such modifications and, further, provide an expectation of success *not found* in the cited references that such a modification will be produce a PKS encoding epothilone derivatives.

In addition to not providing motivation to make a PKS comprising a modified EpoD protein that lacks certain β-carbonyl modifying activities, the references relied on by the Office provided no expectation of success. The Office asserts the cited references taken together "would have provided one of ordinary skill in the art with motivation and *expectation of success* to make derivatives of epothilone which would be very difficult to obtain by organic synthesis [emphasis added]."

However, both the motivation to modify, and any expectation of that modification of a synthase protein will be successful (i.e., will produce "derivatives of epothilone which would be very difficult to obtain by organic synthesis"), requires an understanding of the properties of the epothilone synthase. As discussed above, the teachings of the Schupp reference would not have provided an expectation of success because (1) there is no teaching as to what epothilone would be produced by the unmodified PKS, and (2) there is teaching away from the expectation that derivatives of epothilone D (taught by the present inventors) would be produced by a PKS comprising a modified EpoD protein. Applicants respectfully submit that a combination of references, which the Examiner asserts (but the Applicants do not concede) together merely suggest that modifications in the epothilone synthase *can* be made, does not render obvious the specific modified PKSs taught by the present inventors to produce derivatives of epothilone D.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicants have, by way of the amendments and remarks presented herein addressed all issues that were raised in the outstanding Office Action. Applicants respectfully submit that this Amendment has demonstrated there is no legal basis for the rejections and so that the pending claims are in condition for allowance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 300622003110. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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